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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/823,973 | 04/14/2004 | James J. Gibbons JR. | AM-101323USA | 5335 |

38199 7590 11/29/2006

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|---|---|
| FETTEROLF, BRANDON J | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1642 | |

DATE MAILED: 11/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/823,973 | GIBBONS ET AL. | |
| | Examiner | Art Unit | |
| | Brandon J. Fetterolf, PhD | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *15 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *3-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 25-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Response to the Amendment*

The Amendment filed on 09/15/2006 in response to the previous Non-Final Office Action (6/22/2006) is acknowledged and has been entered.

Claims 1-30 are currently pending.

Claims 3-24 are withdrawn from consideration as being directed to non-elected species.

Claims 1-2 and 25-30 are currently under consideration

**The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.**

**Rejections Maintained:**

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-2, 25-26 and 28 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Muss et al. (J. Clinical Oncology 1987; 5: 286-291) in view of Raymond et al. (Proceedings of ASCO 2000; 19: 187a, IDS).

Muss et al. teach a method of treating renal cell carcinoma comprising administering a therapeutically effective amount of interferon alpha (Title and page 287, 1st column, *IFN Preparation and Study Design*). Specifically, the reference teaches a modest but definite antitumor effect of interferon alpha in advanced renal cell carcinoma.

Muss et al. do not explicitly teach the combination of CCI-779 and interferon alpha for the treatment of renal cell carcinoma or a pharmaceutical pack/composition comprising CCI-779 and interferon alpha.

Raymond et al. teach the antitumor effect of the Rapamycin analog, CCI-779. Specifically, the reference teaches a method of treating renal carcinoma comprising administering CCI-779 to a patient (2nd column, abstract 728, 7th line from bottom).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to treat renal cell carcinoma because each of the therapeutics had been individually taught in the prior art to be successful at treating renal cell carcinoma. The instant situation is amenable to the type of analysis set forth in In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant claims, one of ordinary skill in the art would have reasonable expectation of success that by administering a combination of interferon alpha and CCI-779 to a patient suffering from renal cell carcinoma, one would achieve a method of treating renal cell carcinoma in a patient in need thereof.

Secondly, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983).

In response to this rejection, Applicants assert that claims 1, 2, 25, 26 and 28 are drawn to a method of treating renal cancer by administering a composition comprising CCI-779 (a rapamycin derivative) and IFN-$\alpha$, and a pharmaceutical pack containing the same. Moreover, Applicants assert

that they have clearly demonstrated that the combination of CCI-779 and IFN-α is efficacious for treating renal cancer and further, that the combination of CCI-779 and IFN-α was able to impart tumor regression as opposed to retarding the growth of tumors, as was observed when CCI-779 and IFN-α were administered individually. Applicants further assert that they have demonstrated unexpected results because a synergistic effect was observed by administering CCI-779 and IFN-α for the treatment of renal cancer (see, for example, the specification at page 13, lines 19-22). In addition to the unexpected results, Applicants assert that there is no expectation of success for combining Muss et al., in view of Raymond et al. to arrive at the instant invention in light of the prior art (FDA Guidelines) and knowledge well-known to persons of ordinary skill in the art. Applicants assert that in the FDA guidelines it is clearly recognized that drug-drug interaction are a major concern when administering more than one drug (see, for example, page 3). In light of this document and well-known principles of pharmacokinetics, Applicants assert that there is no reasonable expectation of success for combining CCI-779 and IFN-α for treating renal cancer. For example, Applicants assert that the in vivo absorption, distribution, metabolism, and/or elimination of CCI-779 may be partially or completely altered resulting in the drug efficacy being substantially affected or completely abolished in the presence of IFN-α, which displays its intrinsic properties related to in vivo absorption, distribution, metabolism, and elimination. As such, Applicants assert that there is no reasonable expectation of success when combining Muss et al. in view of Raymond et al. to arrive at the instant invention; and that there the necessary motivation to combine Muss et al. in view of Raymond et al. is not met in this case. In addition, Applicants assert that all the limitations of the claims, e.g., sub therapeutically effective amounts of CCI-779 and IFN-α, are not met by Muss et al. in view of Raymond et al.

These arguments have been carefully considered, but are not found persuasive.

In response to Applicants assertions of unexpected results, e.g., synergistic activity, the Examiner acknowledges that the specification teaches that data presented in Table 1 shows that CCI-779 and IFN-a are synergistic in the test procedure in that they were able to achieve an effect (tumor regression) not attainable with single agent treatment (specification, page 13, last paragraph). However, the Examiner recognizes that the claims are drawn to treating a neoplasm in a mammal in need thereof, which comprises providing to a mammal an effective amount of a combination

comprising CCI-779 and interferon a. As such, the features upon which applicant relies (i.e., synergistic) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Regarding Applicants assertions with respect to no expectation of success for combining the references in light of the FDA guidelines and knowledge well-known to persons of ordinary skill in the art, the Examiner acknowledges and appreciates Applicants submission of the FDA guidelines which teach that drug-to drug interactions are a concern when administering more than one drug. However, the Examiner recognizes that the submitted FDA guidelines "reflects the Agency's current view that the metabolism of an investigational new drug should be defined during drug development and that its interactions with other drugs should be explored as part of an adequate assessment of its safety and effectiveness." (page 1, 1st paragraph) (emphasis added). In contrast to the FDA guidelines pertaining to new investigational drugs, both interferon alpha and CCI-779 have been individually taught in the prior art to be successful at treating renal cell carcinoma and the courts have held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art, *see* In re Kerkhoven,205 USPQ 1069 (CCPA 1980). Regarding Applicants assertions that the action did not meet all the limitations such as a sub-therapeutically effective amount of CCI-779 and IFN-a, the Examiner acknowledges that the references do not explicitly state a sub-therapeutical dose of CCI-779 and IFN-a. However, the Examiner recognizes that the dosages disclosed by Muss et al. and Raymond et al. are construed as subthearpeutic because the claims do not appear to specifically limit what a "subtherapeutically effective dose" is. Therefore, claims 1-2, 25-26 and 28 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Muss et al. (J. Clinical Oncology 1987; 5: 286-291) in view of Raymond et al. (Proceedings of ASCO 2000; 19: 187a, IDS).

Claims 27 and 29-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Laurent et al. (European J. Cancer 1994; 30A: 1859-1865) in view of Beuvink et al. (Proc. Am. Assoc. Cancer Res. 2001; 42: 366 (abstract 1972)).

Laurent et al. teach the antitumor effects of interferon alpha as a single agent and in combination with 5'-deoxy-5-fluorouridine on xenograft tumors. Specifically, the reference teaches

that administration of interferon alpha alone significantly inhibited tumor growth (abs). Moreover, Laurent et al. teach that the combination of interferon alpha and 5'-deoxy-5-fluorouridine resulted in an enhanced antitumor activity (Abs).

Laurent et al. do not explicitly teach the combination of RAD001, e.g., 42-O-(2-hydroxy)ethyl rapamycin, and interferon alpha for the treatment of xenograft tumors or a pharmaceutical composition comprising interferon alpha and RAD001, e.g., 42-O-(2-hydroxy)ethyl rapamycin.

Beuvink et al. teach a method inhibiting the growth of human tumor xenografts in nude mice comprisign administering a therapeutically effective amount of RAD001, e.g., 42-O-(2-hydroxy)ethyl rapamycin.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to treat xenograft tumors because each of the therapeutics had been individually taught in the prior art to be successful at inhibiting the growth of xenograft tumors. The instant situation is amenable to the type of analysis set forth in In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant claims, one of ordinary skill in the art would have reasonable expectation of success that by administering a combination of interferon alpha and RAD001, e.g., 42-O-(2-hydroxy)ethyl rapamycin, one would achieve a successful method of inhibiting the growth of xenografted tumors.

Secondly, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983).

In response to this rejection, Applicants assert that for the reasons articulated in the response to the rejection predicated on Muss et al. in view of Raymond et al., the combination of Laurent et al. in view of Beuvink et al. also fails to supply the necessary motivation to combine these

documents and the reasonable expectation of success required to establish a prima facie case of obviousness.

These arguments have been carefully considered, but are not found persuasive for the reasons articulated in the response to Applicants arguments pertaining to Muss et al. in view of Raymond et al.

Therefore, NO claim is allowed

**All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.**

***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Patent Examiner
Art Unit 1642

BF

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SUPERVISORY PATENT EXAMINER